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PATENT

Attorney Reference Number 6395-59041-01
Application Number 09/889,317

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Tripp et al.

Application No. 09/889,317

Filed: July 13, 2001

Confirmation No. 2319

For: METHOD FOR THE PREVENTION AND
TREATMENT OF DISEASES CAUSED
BY AN INFLAMMATORY RESPONSE
MEDIATED BY ENDOGENOUS
SUBSTANCE P BY USING ANTI-
SUBSTANCE P ANTIBODIES

Examiner: Francois P. Vandervegt

Art Unit: 1644

Attorney Reference No. 6395-59041-01

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Attorney or Agent
for Applicant(s)

Date Mailed

March 16, 2006

DECLARATION OF DR. TRIPP UNDER 37 C.F.R. §1.132

1. I, Ralph A. Tripp, am an inventor of the above-referenced patent application. I was employed by the Centers for Disease Control and Prevention, the assignee of the above-identified pending patent application. I hold a Ph.D. degree in immunology, and have expertise in RNAi therapeutics, innate and adaptive immune responses to respiratory viral infections, cytokines, chemokines and host cell defense mechanisms. I was employed by the Centers for Disease Control and Prevention for 7 years studying the mechanisms of immunity and disease pathogenesis associated with respiratory virus infections.

2. I have reviewed the specification of the above-referenced application, and the Office action, dated April 8, 2005. It is my understanding that claims 1-3, 5, 13, 14, 19-22, 31, 32, 37, 38, and 41-42 have been rejected as allegedly being obvious.

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3. As stated in my Declaration submitted on August 5, 2005, a major limitation in the effectiveness of monoclonal antibodies is immunogenicity of the monoclonal antibody itself; the development of an inflammatory reaction following administration can significantly limit the usefulness of an antibody. The immunogenicity of antibodies that specifically bind an antigen of interest (such as substance P), or fragments of this antibody, cannot be reliably predicted. In addition, the route of administration can affect the immunogenicity of an antibody; the effect of the route of administration on immunogenicity also must be determined experimentally.

4. Hemmingson et al. (Scand. J. Infect. Dis. 25(6): 783-985, 1993) describes that the nasal administration of non-specific immunoglobulins, mainly IgA, could be used for short-term physiological prophylaxis for the prevention of upper respiratory tract infections (colds) in healthy skiers. An upper respiratory tract infection (the common cold) is different from an infection with respiratory syncytial virus (RSV). RSV is a pathogenic agent (a virus) that induces lung inflammation, and can cause significant morbidity and mortality in preterm infants and young infants with chronic lung disease.

Currently, there are only two options for immunoprophylaxis for preventing respiratory syncytial virus (RSV) infection in infants. Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) is a polyclonal hyperimmune globulin prepared from donors selected for having high serum titers of RSV neutralizing antibody. SYNAGIS® (PALIVIZUMAB) is a humanized murine monoclonal anti-F glycoprotein IgG₁ antibody with neutralizing and fusion inhibitory activity against RSV. Both of these compositions are approved for use in the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease.

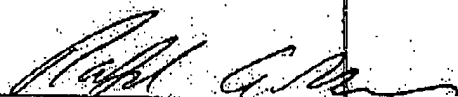

These compositions are administered either intramuscularly or intravascularly. Specifically, SYNAGIS® is supplied as a sterile, preservative free solution, and can be administered by intramuscular injection only. A copy of the package insert for SYNAGIS® is attached as Exhibit A. RSV-IGIV prophylaxis requires intravenous access, and is administered intravascularly as a 4-hour infusion. A copy of a printout from the British Columbia Ministry of Health describing RSV-IGIV administration is attached as Exhibit B.

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Data on the effect of the route of administration (intranasal versus intraperitoneal) of F(ab)₂ anti-substance P antibodies fragments was presented in the Declaration of Ralph A. Tripp Under 37 C.F.R. § 1.132, that was submitted to the U.S. Patent and Trademark Office on August 5, 2005. The data presented therein documents an unexpectedly superior effect when F(ab)₂ anti-substance P antibodies fragments were administered intranasally (as compared to intraperitoneal administration). The two commercially available products for the prevention of lung inflammation caused by RSV are administered systemically by injection (either intravascular or intramuscular injection). In view of the prior routes of administration, one of skill in the art would have predicted a systemic route of administration, such as intramuscular, intraperitoneal, or intravenous administration, would be more efficacious and have less unwanted side effects than an intranasal route of administration for the treatment of a lung inflammatory disorder.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.


Ralph A. Tripp
Date

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SYNAGIS® (PALIVIZUMAB) for Intramuscular Administration

Rx only

DESCRIPTION: Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1) produced by recombinant DNA technology directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis is a recombinant of human (55%) and murine (45%) antibody sequences. The human heavy chain sequence was derived from the constant domain of human IgG1 and the variable framework regions of the V_H genes C1 and C2. The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L genes K104 and K105 (3). The murine sequences were derived from a murine monoclonal antibody, M2129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody framework. Synagis is composed of two heavy chains and two light chains and has a molecular weight of approximately 144,000 Daltons.

Synagis is available in two formulations: a lyophilized powder and a liquid solution.

Lyophilized Powder: Synagis is supplied as a sterile lyophilized powder for reconstitution with sterile water for injection. Reconstituted Synagis (100 mg/mL) is to be administered by intramuscular injection (IM) only. The reconstituted solution should appear clear or slightly opalescent with a pH of 6.0.

Each 100 mg single-use vial of Synagis lyophilized powder is formulated in 67.5 mg of mannitol, 0.7 mg histidine and 0.3 mg of glycine and is designed to deliver 100 mg of Synagis in 1.0 mL when reconstituted with 1.0 mL of sterile water for injection. Each 50 mg single-use vial of Synagis lyophilized powder is formulated in 40.5 mg mannitol, 0.3 mg histidine and 0.2 mg of glycine and is designed to deliver 50 mg of Synagis in 0.5 mL when reconstituted with 0.5 mL of sterile water for injection.

Liquid Solution: Synagis (100 mg/mL) is supplied as a sterile, preservative-free solution to be administered by intramuscular injection (IM) only. The solution should appear clear or slightly opalescent with a pH of 6.0.

Each 100 mg single-use vial of Synagis liquid solution is formulated in 4.7 mg of histidine and 0.1 mg of glycine in a volume of 1.2 mL and is designed to deliver 100 mg of Synagis in 1.0 mL.

Each 50 mg single-use vial of Synagis liquid solution is formulated in 2.7 mg of histidine and 0.06 mg of glycine in a volume of 0.7 mL and is designed to deliver 50 mg of Synagis in 0.5 mL.

CLINICAL PHARMACOLOGY: Mechanism of Action: Synagis exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis (5). Synagis serum concentrations of 240 µg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredients in Synagis was assessed in a randomized, placebo-controlled study of 35 pediatric patients (mostly hospitalized because of RSV disease). In these patients, Synagis significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In pediatric patients <24 months of age without congenital heart disease (CHD), the mean half-life of Synagis was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean \pm SD 30 day trough serum drug concentrations of 27 \pm 21 µg/mL after the first injection, 57 \pm 41 µg/mL after the second injection, 48 \pm 31 µg/mL after the third injection and 72 \pm 30 µg/mL after the fourth injection (7). Trough concentrations following the first and fourth injections were similar in children with CHD and in non-cardiac patients. In pediatric patients given Synagis for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 µg/mL and 86 \pm 31 µg/mL, respectively.

In 129 pediatric patients <24 months of age with hemodynamically significant CHD who received Synagis and underwent cardiopulmonary bypass for open-heart surgery, the mean \pm SD serum Synagis concentration was 98 \pm 52 µg/mL before bypass and declined to 41 \pm 22 µg/mL after bypass, a reduction of 58% (see **DOSEAGE AND ADMINISTRATION**). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis systemic exposure. However, no effects of gender, age, body weight or race on Synagis serum trough concentrations were observed in a clinical study with 339 pediatric patients with CHD (524 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis. Trough serum Synagis concentrations were comparable between the Synagis liquid and Synagis lyophilized formulations administered IM at 15 mg/kg in a cross-over trial in 15 pediatric patients 56 months of age with a history of prematurity.

CLINICAL STUDIES: The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1502 patients 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (35 weeks gestational age) who were <6 months of age at study entry (7). Trial 2 was conducted over four consecutive seasons during a total of 1287 patients 24 months of age with hemodynamically significant congenital heart disease. In both trials, participants received 15 mg/kg Synagis or an equivalent volume of placebo IM monthly for five injections over 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 94% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction	p-Value
Trial 1	n	500	1002			
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%	<0.001
Trial 2	n	648	639			
	Hospitalization	63 (9.7%)	34 (5.3%)	6.4%	45%	0.003

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (38/266 [12.8%] placebo vs. 34/246 [13.8%] Synagis) and in premature infants without BPD (19/224 [8.5%] placebo vs. 33/68 [11.9%] Synagis). In Trial 2, reductions were observed in premature (16/305 [5.2%] placebo vs. 15/406 [3.7%] Synagis) and congenital heart disease (27/343 [7.9%] placebo vs. 14/339 [4.1%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients who received Synagis compared to those who received placebo.

INDICATIONS AND USAGE: Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) (see **CLINICAL STUDIES**).

CONTRAINDICATIONS: Synagis should not be used in pediatric patients with a history of severe prior reaction to Synagis or other components of the product.

WARNINGS: Very rare cases of anaphylaxis (≤1 case per 100,000 patients) have been reported following re-exposure to Synagis (see **ADVERSE REACTIONS**). Patients with a history of severe hypersensitivity reactions have also been reported on initial exposure to re-exposure to Synagis. If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If further hypersensitivity reactions occur, caution should be used in re-administration of Synagis. If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.

PRECAUTIONS: General: Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution in patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis does not contain a preservative. Lyophilized Synagis may be used within 6 hours of reconstitution. Administration of either reconstituted Synagis or liquid Synagis should occur immediately after withdrawal from vial. The vial should not be re-entered. Discard any unused portion.

Drug Interactions: No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchiolitis or coxsackievirus were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Concomitant Administration: Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

Pregnancy: Frequency Category C: Synagis is an IgG antibody that is administered to adult usage and animal reproduction studies have not been conducted. It is not known whether Synagis can cause fetal harm when administered to a pregnant woman or to a fetus.

ADVERSE REACTIONS: The most serious adverse reactions occurring with Synagis treatment are anaphylaxis and other acute hypersensitivity reactions (see **WARNINGS**). The adverse reactions most commonly observed in Synagis-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Other respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of this drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice. The use and a basis for extrapolating rates.

The data described reflect Synagis exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trial 1 and 2. Among these patients, 496 had hemodynamically significant CHD, 500 were premature birth infants less than 6 months of age, and 639 had congenital heart disease. Adverse events observed in the 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the two formulations, and similar to the adverse events observed with Synagis in Trial 1 and 2.

Table 2: Adverse Events Occurring at a Rate of 1% or Greater More Frequently in Patients Receiving Synagis (palivizumab)

Event	Synagis® (n=1641) n (%)	Placebo (n=1407) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	537 (32.6)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	429 (26.8)	282 (24.6)
Diarrhea	68 (4.1)	30 (2.6)
SCOT increase	43 (3.0)	20 (1.7)

*Synagis (Synagis) (3.1%)(placebo (3.9%)) and anaphylaxis (Synagis) (3.1%)(placebo (1.7%)) were reported during Trial 2 in CHD patients.

Immunogenicity

In Trial 1, the incidence of anti-Synagis antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In pediatric patients receiving Synagis for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying medical disease. For these reasons, comparison of the incidence of antibodies to Synagis with the incidence of antibodies to other products may be misleading.

Pharmacokinetics

The following adverse reactions have been identified and reported during post-approval use of Synagis. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure (see **WARNINGS**). None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotension and coma. The relationship between these reactions and the development of antibodies to Synagis is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a second or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

OVERDOSEAGE: No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis at a dose of 50 mg/kg.

DOSEAGE AND ADMINISTRATION: The recommended dose of Synagis is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardiopulmonary bypass (see **CLINICAL PHARMACOLOGY**). Patients undergoing cardiopulmonary bypass should receive a dose of Synagis as soon as possible after the cardiopulmonary bypass procedure (even if sooner than 6 months from the previous dose). Therefore, doses should be administered monthly. Synagis should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the gluteal muscle of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight (kg) x 15 mg/kg x 100 mg/mL of Synagis. Injection volumes over 1 mL should be given as divided doses.

Preparation of Lyophilized Product for Administration

- To reconstitute, remove the top portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 mg or 100 mg Synagis, respectively when reconstituted following the directions described below.
- SLOWLY** add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be tilted slightly and gently rotated for 30 seconds to allow foaming. **DO NOT SHAKE or VIGOROUSLY AGITATE** the vial. This is a critical step to avoid prolonged foaming.
- Reconstituted Synagis should stand undisturbed at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis should be inspected visually for particulate matter or discoloration prior to administration. The reconstituted solution should appear clear or slightly opalescent (a thin layer of micro-bubbles on the surface is normal and will not affect dosing). **DO NOT USE** if there is particulate matter or if the solution is discolored.
- Reconstituted Synagis does not contain a preservative and should be administered within 6 hours of reconstitution. Administer immediately after withdrawal from vial. Synagis is supplied in single-use vials. **DO NOT RE-ENTER** the vial. Discard any unused portion.

Preparation of Liquid Product for Administration

- Remove the top portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 mg or 100 mg Synagis.
- Synagis does not contain a preservative and should be administered immediately after withdrawal from vial. Synagis is supplied in single-use vials. **DO NOT RE-ENTER** the vial. Discard any unused portion.
- To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, use disposable syringes and needles should be used. **DO NOT REUSE** syringes and needles.

HOW SUPPLIED

Synagis is available in two formulations: a lyophilized powder and a liquid solution.

Lyophilized Powder: Synagis is supplied in single-use vials as lyophilized powder to deliver either 50 mg or 100 mg Synagis when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1 Upon reconstitution the 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4111-1 Upon reconstitution the 100 mg vial contains 100 mg Synagis in 1.0 mL.

Liquid Solution: Synagis is supplied in single-use vials as a preservative-free, sterile solution at 100 mg/mL in 0.5 mL and 1.0 mL to deliver either 50 mg or 100 mg Synagis, respectively, for IM injection.

50 mg vial NDC 60574-4114-1 The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1 The 100 mg vial contains 100 mg Synagis in 1.0 mL.

Upon receipt and until use, Synagis should be stored between 2°C and 8°C (36°F and 46°F) in its original container. **DO NOT FREEZE.** **DO NOT USE** beyond the expiration date.

REFERENCES

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Gaithersburg, MD 20878
U.S. Govt. License No. 1253
(1-877-633-4411)

Co-Manufactured by:
ROSS BIOSCIENCES CORPORATION
10000 WILSON AVENUE
ANN ARBOR, MI 48106-1500

EXHIBIT

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RSV-IGIV to prevent RSV infection

Examples

Brand Name	Chemical Name
RespiGam	respiratory syncytial virus immune globulin intravenous (RSV-IGIV)

How It Works

RSV-IGIV is used to help prevent or decrease complications of respiratory syncytial virus (RSV) infection, such as pneumonia and bronchiolitis. RSV-IGIV is made up of several proteins (antibodies) obtained from many human blood donors. The antibodies were created by the donors' natural defence (immune) systems to fight RSV.

RSV-IGIV is given through a vein (intravenous, or IV) in monthly doses for the entire RSV season (usually from November through March). It is given over about 4 hours in a hospital or doctor's office or at home.

Why It Is Used

RSV-IGIV is given only to help prevent RSV in children who have a high risk of developing complications. Palivizumab, another type of monoclonal antibody used for this purpose, is generally preferred over RSV-IG. However, either medication can be given for children at risk for RSV complications who:

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- Have chronic lung disease (CLD), also sometimes called bronchopulmonary dysplasia, and are currently younger than 24 months. The child must have received treatment for the lung disease within the previous 6 months.
- Were born at least 8 weeks prematurely regardless of whether they have CLD. These children may benefit from treatment until they are 6 to 12 months old.
- Were born 5 to 8 weeks prematurely and have at least one additional risk factor. Palivizumab is considered for these babies on an individual basis. Additional risk factors include babies who:
 - Weighed less than expected at birth (low-birth-weight infants) and have other health problems that place them at risk.
 - Live in a home with other young children.
 - Go to child care centres.
 - Are exposed to tobacco smoke.
- Have impaired immune systems from diseases (such as AIDS) or take medication that suppresses the immune system, such as chemotherapy or steroids.¹

This medication is not an effective treatment for children already infected with RSV. It should also not be given to children who have a cyanotic congenital heart defect.

How Well It Works

RSV-IGIV provides moderate protection for babies.² RSV-IGIV has shown to reduce admission rates to hospitals in children born prematurely, in children with chronic lung disease, and in children with a combination of risk factors.³

Side Effects

Side effects of RSV-IGIV are uncommon but can include:

- Allergic reaction.
- Fever.
- Nausea and vomiting.
- Pulmonary edema.

Although there is a potential for contracting HIV infection, hepatitis, or other diseases from the blood product that makes up RSV-IGIV, the risk is extremely rare. All blood donors are carefully screened and blood products are treated for viruses. This process has virtually completely eliminated any risk of exposure from RSV-IGIV.


What To Think About

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Immunizations with measles-mumps-rubella (MMR) and chicken pox vaccines should not be given for 9 months after the last dose of RSV-IGIV. The medication prevents the child from developing antibodies to these vaccines. Other immunizations should be given as scheduled according to the childhood immunization schedule. Children who receive RSV-IG do not need an extra dose of any vaccine beyond the normal recommendations. 4

Palivizumab, another type of antibody used to prevent RSV in high-risk babies, may be preferred over RSV-Cry. A child taking palivizumab can be immunized against other diseases without waiting.

Preventive treatment with RSV-IG should continue throughout the RSV season, regardless of whether a child develops RSV. Different strains of RSV can circulate within a community during the same year, so treatment with RSV-IG may still offer protection from infection.

Complete the new medication information form (PDF)  (What is a PDF document?) to help you understand this medication.

Author: Amy Fackler, MA
Merrill Hayden

Updated November 8,
2004

Medical Review: Tom Bailey, MD - Family Medicine
Michael J. Sexton, MD - Pediatrics
Marvin Turk, MD - Infectious Diseases

 **Printer-Friendly**

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